DETAILED ACTION

Election/Restrictions

An earlier Action acknowledged Applicant's election with traverse of Group IV, claim(s) 4-6, 9, 10, 16, 19, 96, and 98, drawn to a method for the treatment of an eye disorder comprising administering a therapeutically effective amount of a dsRNA and detecting a product of the target gene of said dsRNA.

Applicant is advised the Requirement for Restriction to one of the methods of claims 94-97 as set forth in the Requirement mailed 4/4/2008 is hereby withdrawn. Claims 94, 95, and 97 are rejoined with the elected invention for examination on the merits.

Status

Applicant's amendment to the claims filed 6/3/2009 is acknowledged. With entry of the amendment, claims 1, 4-6, 9, 16, and 94-99 are pending and examined herein.

Applicant's response filed 6/3/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/3/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Domestic and Foreign Priority

The previous Action explained that written description support is not found in either of the domestic or foreign priority documents for the claimed invention. In particular written description and/or enabling support is not found in Provisional Application 60/431172 or Foreign Priority Application EP02008761.5 for a method of treating RPE, neurosensory retina, choroid,

AMD, or diabetic retinopathy by administration of dsRNAs. Further, no support is found in either of the prior filed applications for interfering dsRNAs targeting SEQ ID NO:3, or for methods of treatment further comprising detecting the product of the target gene.

To be entitled to the benefits of 35 U.S.C. 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Thus, with entry of the amendment filed 10/15/2008, the disclosure of the prior-filed application, Application No. 60/431,173 and EP 02008761.5 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for claims 1, 4-6, 9, 16, 96, and 98. For at least the same reasons given above, no support is found in these prior filed applications for new claim 99.

Thus, for purposes of this examination, the earliest effective filing date of claims 1, 4-6, 9, 16, 96, 98, and 99 is considered to be that of PCT/EP03/04003, filed 4/16/03.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 9, 16, and 94-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

Upon further consideration, the instant application as filed is not considered to reasonably enable one of skill at the time of filing to use the methods now claimed for treating an eye disorder in a subject by interfering with the expression of SEQ ID NO:3 without resorting to substantial *de novo* trial and error experimentation with no assurance of every reaching a successful conclusion, since there is no evidence remotely connecting the claimed method with the treatment of any eye disorder and no direction or guidance as to how to achieve the claimed effects other than a general invitation to try. A reasonable correlation between the inhibition of SEQ ID NO:3 and the treatment of any eye disorder, much less those specifically intended by the claims, has not been established. Thus, the scope of the claims is not commensurate with the application as filed.

The claims are drawn to methods of treating a disorder of the eye, comprising administering to a subject a short interfering double stranded RNA complementary to the mRNA sequence of SEQ ID NO:3. For purposes of this examination the preamble is given the import that the claim as a whole suggests for it. Thus, for purposes of this rejection the methods are considered to require treatment of an eye disorder in the subject to which the dsRNA is administered—i.e., the preamble is a statement of the intentional purpose for which the method must be performed (See MPEP 2111.02.II). Although the body of the claim does not specifically refer to elements or limitations in the preamble, the limitation "administering to a subject a therapeutically effective amount of a composition" implies the subject is one with a recognized need to treat an eye disorder

In certain claimed embodiments the disorder is one related to angiogenesis, neovascularization, retinal pigment epithelium (RPE), neurosensory retina, choroid, or any

combination thereof. In other claimed embodiments the disorder is specifically wet-age macular degeneration, diabetic retinopathy, autosomal recessive retinitis pigmentosa, or cogenital stationary night blindness.

The specification teaches and the extrinsic literature confirms that SEQ ID NO:3, a 3231-nucleotide DNA, corresponds to human phosphodiesterase 6B, cGMP-specific, rod, beta (PDE6B) mRNA (accession No. NM_000283). The specification teaches and the extrinsic evidence confirms that malfunction of this gene, and more specifically, missense or nonsense mutations in this gene are associated with autosomal recessive retinitis pigmentosa, or congenital stationary night blindness 3 (CSNB3). See, for example, Dryja et al. (1995) "Mutations in the gene encoding the alpha subunit of the rod cGMP-gated channel in autosomal recessive retinitis pigmentosa" *PNAS* 92:10177-10181. Weber et al. (1991) "Genomic organization and complete sequence of the human gene encoding the 3-subunit of the cGMP phosphodiesterase and its localisation to 4p16.3" *Nucleic Acids Res.* 19:6263-6268 (of record), also taught that the conditions associated with autosomal recessive retinitis pigmentosa (RP) stem from an insufficiency of cGMP phosphodiesterase not an overabundance, stating at page 6267 that:

> Recently, evidence has been provided that the degenerative process in the retinal degeneration (rd) mouse is caused by a defect in the β-subunit of the rod cGMP PDE (8). The rd mouse is considered an animal model for autosomal recessive retinitis pigmentosa (RP) as homozygous mice have been shown to display hereditary progressive degeneration of retinal photoreceptors (36, 37). Retinal degeneration in these mice is preceded by elevated levels of cGMP in the retina as a result of deficient cGMP PDE activity (38, 39).

Hart et al. (2005) "Genotype–Phenotype Correlation of Mouse *Pde6b* Mutations" *Investigative Ophthalmology and Visual Science*. 2005;46:3443-3450 (post filing art) teaches that defects in photoreceptor phosphodiesterase activity caused by mutations in the ß subunit of

the rod cGMP-phosphodiesterase (*PDE6B*) gene have been shown to underlie cases of arRP accounting for ~1% to 2% of all cases of RP. It is further taught the product of *Pde6b* contributes to the heterotetrameric phosphodiesterase complex (PDE, $\alpha\beta\gamma_2$), which regulates cytoplasmic cGMP levels in rod photoreceptors in response to light. On light stimulation, PDE is activated by removal of the γ-inhibitory subunits, resulting in a decrease in cGMP levels and hyperpolarization of the rod cell. In mice with the retinal degeneration 1 (*rd1*) mutation elevated cGMP levels persist because of a homozygous null mutation in the *Pde6b* gene. This results in permanent opening of cGMP-gated cation channels in the membrane of the rod photoreceptors, allowing an excess of extracellular ions to enter the cell, which ultimately leads to cell death by apoptosis.

Altogether, then, the evidence suggests that further suppressing the expression of PDE, as in the method now claimed, would only further exacerbate the night blindness or retinitis pigmentosa present in the subject. It is unclear then how the claimed method may be used to treat any eye condition, such as any of those claimed, particularly congenital autosomal recessive retinitis pigmentosa or congenital stationary night blindness.

In fact studies published prior to and after the filing date of the instant application show that suppressing the expression of rod cGMP phosphodiesterase subunits in animals using either ribozymes or antisense oligonucleotides actually lead to photoreceptor and bipolar cell degeneration, conditions associated with retinitis pigmentosa. Indeed researchers have used antisense and ribozyme-mediated degradation of the genes encoding either the gamma or alpha subunits of rod cGMP-gated channel protein, a cGMP phosphodiesterase, to produce animal models of human retinitis pigmentosa. See, for example, Liu et al. (2005) "Ribozyme

Knockdown of the [gamma]-Subunit of Rod cGMP Phosphodiesterase Alters the ERG and Retinal Morphology in Wild-Type Mice" *Investigative Opthalmology & Visual Science* 46:3836-3844; and Leconte et al. (2000) "Impairment of rod cGMP-gated channel alpha-subunit expression leads to photoreceptor and bipolar cell degeneration" *Invest Ophthalmol Vis Sci*. 2000 Mar;41(3):917-26.

While the prior and post filing art clearly correlates autosomal recessive retinitis pigmentosa with a deficiency of functional cGMP-gated channels or cGMP phosphodiesterase (PDE) likely caused by certain nonsense and missense mutations in the gene, neither the specification nor the prior or post-filing art teaches or suggests any link between inhibiting the expression of PDE6B (SEQ ID NO:3) or its mutant alleles and the treatment of any eye disease. There is no evidence in the prior art or the specification of any correlation between reducing the expression of SEQ ID NO:3 and any therapeutic effect for any eye disorder. Indeed, the literature teaches that it is not the overexpression of SEQ ID NO:3 or its protein product that leads to RP or any other eye disease but the lack of functional phosphodiesterase protein (i.e., paucity of protein) from SEQ ID NO:3 that may be the cause of RP or night blindness. See, for example, Dryja et al., cited above. Even the name, "autosomal recessive," suggests that RP night blindness disorder associated with SEQ ID NO:3 is not the result of the expression of an abnormal dominant protein but the lack of normal protein essential to eye function. Thus, it is unclear, and the specification does not show or demonstrate, how further repressing the expression of SEQ ID NO:3, as by the method now claimed, would improve the vision or visual acuity of any subject, particularly those having autosomal recessive retinitis pigmentosa or congenital stationary night

blindness. On the contrary it would appear prima facie the expression of the wild type gene should be enhanced or restored to treat the disease.

Furthermore, a review of the specification and the prior art fails to find a single working example showing or adequately representing that inhibiting the expression of an mRNA encoding wild-type or mutant PDE6B (SEQ ID NO:3) produces an effect correlative of treatment in any animal suffering from a disorder of the eye related to angiogenesis, neovascularization, retinal pigment epithelium (RPE), neurosensory retina, choroid, or any combination thereof, wet-age macular degeneration, and diabetic retinopathy. Neither the prior art nor the specification establishes any nexus between the inhibition of SEQ ID NO:3 and the treatment of each of these diseases. Accordingly, it is reasonable to question the objective truth of the assertions in the claims that the administration of an interfering dsRNA targeting SEQ ID NO:3 may be used to treat each of the disorders recited therein. With no examples to draw on and no direction or guidance of any kind in the specification showing how or even whether inhibition of SEQ ID NO:3 or any isoform thereof may be used to treat each of these disorders one of skill would necessarily need to resort to *de novo*, trial and error experimentation to achieve the claimed effects, and with no assurance of ever reaching a successful conclusion. The effects promised by the claims represent hoped-for functions---a starting point for further research, but nothing more. Such research, in the absence of any direction, guidance, or assurance by the specification, is considered to be undue.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to

conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

In response to the previous rejection of claims 4-6, Applicant argues the Office has failed to adequately question the enablement because the Office has failed to provide sufficient evidence to reasonably question the objective truth of the specification and the claims. Applicant argues the Examiner has cited no evidence and makes only conclusory statements.

On the contrary, the Examiner has searched and considered both the specification and the prior art patent and non-patent literature with regard to the assertions made by the claims that inhibiting SEQ ID NO:3 can be used to treat an eye disorder. As explained above, there is no evidence to show or suggest that interfering with the expression of SEQ ID NO:3 would improve any eye condition. In fact, the evidence cited above would suggest that rather than further suppress SEQ ID NO:3, one of skill would look to replacing or restoring the expression of wild type SEQ ID NO:3. Thus, the solution defined by the claims for treating an eye disorder would appear to be contrary to the problem described by the prior art. Other than general statements in the Summary of Invention, the specification provides no direction, examples, or credible evidence suggesting or showing the method as claimed would alleviate or improve conditions in the eye of any subject having any eye disorder directly or even indirectly related to the expression of SEQ ID NO:3. The Examiner submits the complete lack of evidence and direction reasonably correlating and/or showing how the inhibition of SEQ ID NO:3 would result in

treatment of an eye disease is sufficient reason to question the objective truth of the statements in the claims. It is noted MPEP 2164.04, citing *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971), states that it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. In this case the Examiner submits that acceptable reasoning, combined with knowledge in the prior art describing how mutations in a phosphodiesterase gene of SEQ ID NO:3 result in a deficiency of protein that may lead to night blindness, has been set forth to question the objective truth of the statements in the claims.

At the same time, while Applicant argues the examiner has not met the initial burden to establish a reasonable basis to question the enablement, Applicant offers no evidence to counter the basis for questioning the enablement. MPEP 2164.06(c).V. states:

> arguments of counsel may be effective in establishing that an examiner has not properly met his or her burden or has otherwise erred in his or her position. However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure.

Applicant further argues the specification demonstrates the delivery of dsRNA to and inhibition of mRNA in the eye. The Examiner agrees; however, the claims are not drawn to a method of delivering dsRNA to the eye, but to methods of treating an eye disorder. Further, the rationale used here in rejecting the claims for lack of enablement does not concern an inability to deliver but a lack of direction and guidance of the degree necessary to ensure one of skill could, at the time of filing, carry out the method without undue experimentation to achieve the effects asserted by the claims. The Examiner submits the lack of any credible evidence linking the

inhibition of SEQ ID NO:3 with treatment of any eye disorder and the absence of any direction and/or working examples showing one of skill can attain these effects suggests one of skill would need to engage in extensive *de novo* trial and error experimentation to use the method as now claimed.

While the specification enables delivery of a dsRNA to the retinal pigment epithelium and retina of the eye of a subject and RNA interference of a gene in the retinal pigment epithelium and retina of the eye of a subject (see Example 21 at page 52), neither the specification nor the prior art teaches or shows one of skill how to treat any disorder of the eye by specifically inhibiting the expression of *SEQ ID NO:3* in the eye of a subject. Thus, the direction and guidance provided by the specification is not commensurate with the scope of the claims.

It is noted the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue (*In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)). In the instant case the amount of experimentation needed to practice the instant methods would be unduly extensive given the claims cover *any* eye disorder, and many specific disorders, and given there is no evidence or even indirect suggestion that delivery of an interfering RNA complementary to SEQ ID NO:3 will treat any eye disorder in a subject having the disorder, including any of those expressly recited in the claims. Accordingly, the statements of intended use in the specification and the claims amount to mere invitations to conduct research necessary to use the methods as now claimed with no evidence one of skill would ever reach a successful conclusion.

The instant rejection is rebuttable with evidence commensurate in scope with what is now claimed.

Claim Rejections - 35 USC § 103

The rejection of Claims 1, 9, 16, 96, and 98 under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (US Patent 5,814,620) in view of:

1. Dryja et al. (US Patent 5,498,521);
2. Weber et al. (1991) *Nucleic Acids Res.* 19:6263-6268;
3. Collins et al. (1992) "The human beta-subunit of rod photoreceptor cGMP phosphodiesterase: complete retinal cDNA sequence and evidence for expression in brain" *Genomics* 13 (3): 698-704;
4. Epstein (1998) *Methods: A Companion to Methods in Enzymology* 14:21-33;
5. Tuschl et al. (US Patent Application 2004/0259247 A1); and
6. Bass (2001) *Nature* 411:428-9;
7. Tolentino et al. (US Patent 7,148,342); and
8. Pardridge (US 2002/0054902 A1)

is currently withdrawn upon further consideration of the prior art, which does not reasonably suggest or show that inhibiting the expression of SEQ ID NO:3 will result in the treatment of any eye disorder. Applicant's arguments traversing the rejection are therefore presently moot.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
August 10, 2009